**Recipient Comorbidity and Survival Outcomes after Kidney Transplantation: a UK-wide Prospective Cohort Study**

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**Authorship**

All authors contributed to the study design. DAW conducted the literature review. DAW and MLR conducted the data analysis. DAW and GCO drafted the manuscript. All authors interpreted the data, revised the drafts and approved the final version.

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**Abbreviations**

ARD, adjusted risk difference

ATTOM, Access to Transplantation and Transplant Outcome Measures

BMI, body mass index

CI, confidence interval

CIT, cold ischaemia time

CLD, chronic liver disease

cRF, calculated reaction frequency

CVD, cerebrovascular disease

DDKT, deceased-donor kidney transplant

DGF, delayed graft function

ERA-EDTA, European Renal Association – European Dialysis and Transplant Association

ESRD, end-stage renal disease

HF, heart failure

HLA, human leukocyte antigen

HR, hazard ratio

IHD, ischaemic heart disease

LDKT, living-donor kidney transplant

MM, mismatches

PVD, peripheral vascular disease

SE, standard error

UK, United Kingdom

WHO, World Health Organisation

**Abstract**

Background: Comorbidity is increasingly common in kidney transplant recipients, yet the implications for transplant outcomes are not fully understood. We analysed the relationship between recipient comorbidity and survival outcomes in a UK-wide prospective cohort study – ATTOM.

Methods: 2100 adult kidney transplant recipients were recruited from all 23 UK transplant centres between 2011-2013. Data on 15 comorbidities were collected at the time of transplantation. Multivariable Cox regression models were used to analyse the relationship between comorbidity and 2-year graft survival, patient survival and transplant survival (earliest of graft failure or patient death) for deceased-donor kidney transplant (DDKT) recipients (n=1288) and living-donor kidney transplant (LDKT) recipients (n=812).

Results: For DDKT recipients, peripheral vascular disease (HR 3.04, 95%CI 1.37, 6.74, p=0.006) and obesity (HR 2.27, 95%CI 1.27, 4.06, p=0.006) were independent risk factors for graft loss, while heart failure (HR 3.77, 95%CI 1.79, 7.95, p=0.0005), cerebrovascular disease (HR 3.45, 95%CI 1.72, 6.92, p=0.0005) and chronic liver disease (HR 4.36, 95%CI 1.29, 14.71, p=0.018) were associated with an increased risk of mortality. For LDKT recipients, heart failure (HR 3.83, 95%CI 1.15, 12.81, p=0.029) and diabetes (HR 2.23, 95%CI 1.03, 4.81, p=0.042) were associated with poorer transplant survival.

Conclusion: The key comorbidities that predict poorer 2-year survival outcomes after kidney transplantation have been identified in this large prospective cohort study. The findings will facilitate assessment of individual patient risks and evidence-based decision making.

Keywords: kidney transplantation, outcomes, survival prediction, comorbidity

**Introduction**

Kidney transplantation is widely regarded as the treatment of choice for end-stage renal disease (ESRD). However, outcomes after transplantation vary considerably between patients and prediction of individual risk is challenging due to the increasing prevalence of complex comorbidity among the ESRD population. Conditions such as diabetes, hypertension and obesity which contribute to the development of ESRD are on the rise,1 while ESRD itself is an important risk factor for other comorbidities such as cardiovascular disease.2, 3 Over the past decade, the proportion of deceased-donor kidney transplant (DDKT) recipients older than 60 years of age has increased from 17% to 29% in the UK,4 and the burden of comorbidity among patients undergoing kidney transplantation has also risen significantly.5-7

Despite this, there are limited data on the impact of comorbidity on transplant outcomes. A small number of studies have demonstrated the overall detrimental effect of comorbidity on transplant outcomes using various comorbidity indices.5, 8-10 However, this does not allow characterisation of the risks associated with specific comorbid conditions.. Retrospective registry analyses have identified several comorbidities as risk factors for transplant outcomes, but the results show considerable heterogeneity and are limited by the reliability of the data.11-13 Up-to-date and reliable evidence is essential to enable clinicians to fully inform patients of their individual risks and likely outcomes, thereby facilitating shared decision-making and informed consent.

We conducted a national prospective cohort study to investigate the impact of a wide range of baseline comorbid conditions on survival outcomes following kidney transplantation. We report the two-year survival outcomes of the study which was conducted as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme.

**Materials and Methods**

*Study design and participants*

ATTOM is a national prospective cohort study investigating the factors that influence access to and outcomes from renal transplantation in the UK. A full description of the ATTOM protocol has been reported previously.14 A cohort of 2262 incident kidney transplant recipients were recruited to ATTOM at the time of transplantation, from all 23 UK renal transplant centres. In each centre recruitment took place over a 12-month period between 1st November 2011 and 31st March 2013. Patients aged 18-75 years were eligible for recruitment. For the purposes of this analysis, multi-organ transplant recipients (n=162) were excluded. The final study sample (n=2100) represented 73% of eligible study participants from the national kidney-only transplant population (Figure 1). Patients were followed up for two years from the date of transplant. DDKT recipients (n=1288) and living-donor kidney transplant (LDKT) recipients (n=812) were analysed separately.

*Data variables*

The variables of interest were recipient comorbidities at the time of transplantation comprising diabetes, ischaemic heart disease (IHD), heart failure (HF), atrial fibrillation, cardiac valve replacement, pacemaker, cerebrovascular disease (CVD), peripheral vascular disease (PVD), abdominal aortic aneurysm, chronic respiratory disease, chronic liver disease (CLD), blood borne viruses, malignancy, mental illness (definitions given in Supplementary Table S1) and body mass index (BMI).

The primary outcome measures were graft survival, patient survival and transplant survival. Graft survival was defined as the time from transplantation to graft failure (earliest of return to dialysis or re-transplantation), with censoring for death with a functioning graft, at last follow-up or at two years. Patient survival was defined as the time from transplantation to patient death, with censoring at last follow-up or at two years. Transplant survival is a composite outcome defined as the time from transplantation to the earliest of graft failure or patient death, with censoring at last follow-up or at two years.

Potential confounders considered in multivariable analyses included (a) recipient variables: age, gender, ethnicity, primary renal disease (as classified by ERA-EDTA codes15), time on dialysis, previous transplantation, sensitisation level, smoking status; (b) donor variables: age, gender, ethnicity, BMI; (c) transplant variables: human leukocyte antigen (HLA) mismatches (MM), cold ischaemia time (CIT), delayed graft function (DGF). Ethnicity was coded as White, Black, Asian and Other (including Chinese and mixed origin). Recipient calculated reaction frequency (cRF) ≥85% was used to define highly sensitised recipients. The cRF is the percentage of a pool of 10,000 UK donors to whom the recipient has unacceptable HLA antibodies. HLA mismatches were classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme: level 1 (000 HLA-A, B, DR MM), level 2 (0DR + 0/1B MM), level 3 (0DR + 2B MM) or (1DR + 0/1B MM) and level 4 (1DR + 2B MM) or (2DR MM).16

*Data collection*

Baseline recipient variables (including comorbidity) were collected by trained research nurses at the time of transplantation from patient interviews, case notes, local electronic patient information systems and/or confirmed with the patient’s named consultant nephrologist. Independent validation of 5% of data entries in all research sites confirmed >98% concordance for all data fields.14 Donor and transplant variables and 2-year graft and patient survival data were obtained through linkage with the UK Transplant Registry.

*Statistical methods*

Baseline characteristics were compared with chi-squared tests for categorical data and Mann–Whitney U tests for non-parametric continuous data. The impact of comorbidity on two-year survival outcomes was examined using Kaplan-Meier estimates and Cox proportional hazards regression models. DDKT and LDKT recipients were analysed separately. As there were no significant differences in outcomes between recipients of donors after circulatory death and donors after brain death, all DDKT recipients were analysed together. For DDKT recipients, separate multivariable models were built for the three different outcomes of transplant, graft and patient survival. For LDKT recipients, modelling was only possible for transplant survival, as the lower number of graft failures and patient deaths prevented modelling of graft and patient survival separately. All comorbidities were considered for inclusion in the multivariable models, and those leading to a significant (p<0.05) change in log likelihood were retained using a manual backward elimination method. Models were adjusted for statistically significant variables as well as variables selected *a priori* on the basis of clinical relevance. Continuous variables were explored as linear, fractional polynomials and categorical variables. In all models, the effect of the time on dialysis variable was only found to be significant after 3 years, and thus it was converted to a binary variable (<3 years versus ≥ 3 years) as this provided the best fit in each model. The relationship between recipient BMI and graft survival was also found to be better represented by converting BMI to a categorical variable, in accordance with the World Health Organisation (WHO) BMI classifications.17 Potential interactions between all variables were tested, none were significant. The proportional hazards assumption was found to be satisfied for all variables after checking log cumulative hazards plots and Schoenfeld residuals. Frailty models were used to check for inter-centre variation by using the likelihood ratio test to assess the change in -2LogL after inclusion of transplant centre as a random effect. The adjusted risk difference (ARD) was calculated using methods described by Laubender et al.18 The ARD describes the absolute effect of the comorbidity risk factor on survival probabilities after adjustment for covariates in the multivariable model. Standard errors of the ARD were derived from bootstrap methods using 1000 resamples of the data. Patients with missing data were excluded, the extent of missing data is shown in Supplementary Table S2. Sensitivity analyses were conducted to test robustness of the results; each model was adjusted for a risk score developed from UK Transplant Registry data for kidney transplants performed in the 5 years prior to the study recruitment period (2006 - 2011), rather than adjusting for individual confounding factors. This minimised the number of degrees of freedom in the models, and enabled checking for any missed comorbidity effects. All analyses were conducted using SAS® 9.4 (SAS Institute Inc, Cary, USA).

*Ethics approval*

East of England Research Ethics Committee (reference number 11/EE/0120).

**Results**

*Baseline characteristics*

Characteristics of the DDKT (n=1288) and LDKT (n=812) recipients, donors and transplants are shown in Table 1. These were consistent with UK Transplant Registry data for the study recruitment period.19, 20 The demographics of recruited versus excluded patients were compared (Supplementary Table S3). There was a higher proportion of White patients in the recruited group compared with the excluded group, however there were no significant differences in age group, gender or type of transplant. Table 2 shows the prevalence of comorbidity in the study cohort at the time of transplantation. DDKT recipients had significantly higher rates of diabetes (16.0% vs 10.3%, p=0.0002), IHD (9.8% vs 7.0%, p=0.029), HF (3.1% vs 1.6%, p=0.033), CVD (5.8% vs 3.1%, p=0.004) and PVD (3.3% vs 1.7%, p=0.027) compared with LDKT recipients.

*DDKT recipients*

1. *Transplant survival*

Overall, there were 134 “transplant failures” (85 graft failures and 49 patient deaths). The Kaplan-Meier estimate for two-year transplant survival was 89.4% (95% confidence interval [CI] 87.6, 91.0). After adjustment for relevant factors in the multivariable Cox regression model, HF (HR 2.39, 95% CI 1.30, 4.37, p=0.005) and CVD (HR 2.33, 95% CI 1.40, 3.88, p=0.001) were associated with a significant increase in the risk of transplant failure (Table 3). There was no significant inter-centre variation in transplant survival when including transplant centre as a random effect in the model (difference in -2LogL=0.02, degrees of freedom [df]=1, p=0.885). For HF, the ARD was 0.117 (standard error [SE] 0.052) (i.e. patients with heart failure had an 11.7% increased risk of transplant failure within 2 years compared to those without heart failure, after adjustment for all other factors in the multivariable model). For CVD, the ARD was 0.101 (SE 0.043). The effect of adding DGF to the final model is shown in Supplementary Table S4.

1. *Graft survival*

At two years, there were 85 graft failures, and the Kaplan-Meier estimate of graft survival was 93.2% (95% CI 91.7, 94.5). Multivariable Cox regression modelling showed PVD (HR 3.04, 95% CI 1.37, 6.74, p=0.006) and obesity (BMI ≥30.0) (HR 2.27, 95% CI 1.27, 4.06, p=0.006, compared with normal BMI 18.5 – 24.9) to be independent risk factors for graft loss (Table 3). The obesity variable was explored further in the model by dividing it into class I and class II and above (BMI 30.0 – 34.9 and ≥35.0 respectively) (Supplementary Table S5). There were too few patients with obesity class III (BMI ≥40.0) (n=7) to include this as a separate category. There was no significant variation in the risk of graft failure for the different classes of obesity, therefore the broader category of obesity (BMI ≥30.0) was retained in the main model (Table 3). No centre effect on graft survival was found when modelling centre as a random effect (difference in -2LogL=0.23, df=1, p=0.632). Among patients with PVD, the risk of graft failure was highest in the first ten days following transplantation, as demonstrated by the initial steep drop in the survival curve before the more gradual decline (Figure 2A); 85.7% graft failures in the PVD group occurred during this early post-operative period, compared with 26.9% among patients without PVD. In contrast, the impact of obesity on graft survival followed a more gradual decline over the two-year period (Figure 2B). Unadjusted two-year graft survival estimates for patients with and without PVD and obesity are shown in Table 4. The ARD for PVD was 0.104 (SE 0.058) and for obesity was 0.060 (SE 0.029). The incidence of delayed graft function was 31.1% for all patients, 48.7% for patients with PVD and 39.1% for patients with obesity. Adding DGF to the final model resulted in a reduction in the effect of PVD (Supplementary Table S4). The cause of graft failure for all patients as well as patients with PVD and obesity in the DDKT cohort is shown in Table 5.

1. *Patient survival*

There were 56 patient deaths, of which 49 were deaths with a functioning graft. The two-year Kaplan-Meier survival estimate was 95.4% (95% CI 94.1, 96.5). The comorbidities significantly associated with inferior patient survival in the multivariable model included HF (HR 3.77, 95% CI 1.79, 7.95, p=0.0005), CVD (HR 3.45, 95% CI 1.72, 6.92, p=0.0005) and CLD (HR 4.36, 95% CI 1.29, 14.71, p=0.018) (Table 3). There were no significant centre differences in patient survival (difference in -2LogL=0.01, df=1, p=0.925). Among patients with HF and CVD, just over half of patient deaths occurred in the second year after transplantation (55.6% and 58.3% respectively), while 100% of deaths among patients with CLD occurred within the first year post-transplantation. This is demonstrated by the survival curves in Figures 3A, 3B and 3C. Unadjusted 2-year patient survival estimates for patients with and without HF, CVD and CLD are shown in Table 6. For HF, CVD and CLD the ARD was 0.159 (SE 0.057), 0.041 (SE 0.027) and 0.056 (SE 0.091) respectively. The effect of adding DGF to the final model is shown in Supplementary Table S4.

*LDKT recipients*

In the LDKT cohort it was only possible to model transplant survival, as the smaller number of recipients and outcome events prevented meaningful analysis of separate graft and patient survival models. There were 42 “transplant failures” (26 graft failures and 16 patient deaths). The Kaplan-Meier estimate for transplant survival at 2 years was 94.7% (95% CI 92.9, 96.0). The multivariable model demonstrated significantly higher risk of transplant failure for HF (HR 3.83, 95% CI 1.15, 12.81, p=0.029) and diabetes (HR 2.23, 95% CI 1.03, 4.81, p=0.042) (Table 7). There was no significant centre effect on LDKT transplant survival (difference in -2LogL=0.11, df=1, p=0.741). The ARD for HF was 0.121 (SE 0.099) and for diabetes was 0.056 (SE 0.036).

*Sensitivity analyses*

Each multivariable model was checked by adjusting for a risk score (Supplementary Boxes S1, S2, S3 and S4) rather than entering the confounding factors individually into the model (Supplementary Tables S6, S7, S8 and S9). No additional comorbidities were identified as significant, and hazard ratios were very similar to the original models, confirming the reliability of the results.

**Discussion**

In this national observational study, we have collected data prospectively on a wide range of comorbid conditions and identified those that predict poorer survival outcomes after kidney transplantation. Among DDKT recipients, PVD and obesity were associated with a two- to three-fold increased risk of graft failure within two years of transplantation, while the risk of death was three- to four-fold higher with HF, CVD and CLD. For LDKT recipients, HF and diabetes were associated with significant detrimental effects on overall transplant survival, but longer follow up is required to determine the separate effects on graft and patient survival.

Among DDKT recipients, a history of PVD increased the risk of graft failure by 10.4% after adjusting for confounding factors, with the majority of graft failures occurring in the early post-operative period. PVD is typically diagnosed clinically by measuring the ankle-brachial pressure index (ABPI), and our results are in agreement with a US study of 819 patients which reported a 2.77 times increased risk of graft failure for patients with a low ABPI (<0.9).21 Pre-existing PVD affecting the aorta or iliac arteries may complicate implantation of the kidney graft, resulting in difficult anastomoses, cholesterol emboli or hypoperfusion of the graft, and subsequent failure in the early post-operative period.22, 23 Our data showed a high incidence of technical operative issues as the cause of graft failure among PVD patients (42.9%). We also found that the addition of DGF to the regression model for DDKT graft survival reduced the effect of PVD and is thus a potential mediator of this effect. Despite being a high risk group, patients with PVD still derive a significant survival benefit from transplantation compared with dialysis.24, 25 As such, a history of PVD should not preclude transplantation, but given the high risk of early complications, appropriate pre-operative planning and informed consent of patients is crucial.

Obesity is an ongoing topic of controversy with regard to patient suitability for kidney transplantation. Some centres do not exclude patients with obesity, while others restrict access to the waiting list at specific BMI thresholds, which may differ considerably between centres, and even between clinicians within the same centre.26 Despite conflicting outcomes from early single centre studies, more recent meta-analyses have confirmed the detrimental effect of obesity on graft survival.27-30 Our results are in keeping with this evidence; with obesity conferring a 6% increased risk of graft failure among DDKT recipients. The mechanisms for this are unclear. There was a high incidence of acute rejection as a cause of graft failure among obese patients (44%) and this could be a potential cause for the higher risk of graft failure associated with obesity. Difficulties in achieving and maintaining the narrow therapeutic target concentrations of immunosuppressive drugs in obese patients have previously been reported.31

We found that HF was associated with a 15.9% higher risk of mortality after DDKT and 12.1% higher risk of transplant failure after LDKT. We acknowledge that in patients on dialysis, it can be difficult to make a clear distinction between HF and fluid overload; however, our findings demonstrate that a diagnosis of heart failure in the patient’s record predicts poorer survival, irrespective of how the diagnosis was made or the exact pathophysiology. It is also noteworthy that although HF was identified as a significant risk factor, no effect was observed for IHD. Our findings concur with the results of a US study which found that pre-transplant impaired left ventricular systolic function (on single photon emission computed tomography (SPECT)) was associated with a significantly higher risk of both cardiac mortality and all-cause mortality after kidney transplantation, while cardiac ischaemia (on SPECT) was not.32 Our findings suggest that either IHD does not increase the risk of death within two years post-transplantation, or that current risk stratification of patients with IHD in the UK is effective.

CVD was associated with a 4.1% elevated risk of death among DDKT recipients. It is known that patients with ESRD have more severe carotid atherosclerosis than the general population and are at substantially greater risk of stroke.33-35 A large US registry analysis demonstrated that transplantation reduced the risk of cerebrovascular events from 11.8% to 6.8% compared to patients remaining on the waiting list.36 However, previous CVD remains a strong risk factor for further post-transplantation events and mortality.35, 37, 38 Post-transplantation cerebrovascular events are associated with high mortality,39 which is worse for haemorrhagic strokes (48%) compared with ischaemic strokes (6%).38 In a prospective randomised controlled trial including 1652 kidney transplant recipients (ALERT trial), the use of Fluvastatin did not reduce the incidence of cerebrovascular events or mortality.38 Further trials are needed to assess the ability of therapies to reduce the risk of further cerebrovascular events and mortality in this high risk population.

CLD was independently associated with 5.6% increased risk of mortality within two years of DDKT. There is a paucity of published research regarding CLD in kidney transplant outcomes. Previous studies have focussed on the role of hepatitis B and C related liver disease as predictors of increased mortality after kidney transplantation.40-42 The present study is the first to demonstrate that CLD of any aetiology leads to reduced survival after DDKT. Further research is required to understand the underlying mechanisms.

Interestingly, a diagnosis of diabetes was identified as a risk factor for transplant failure among LDKT recipients, but not for DDKT recipients. The reason for this finding is unclear. Diabetes is a well-recognised risk factor for mortality after transplantation, primarily due to elevated cardiovascular risk.43 It may be that this cardiovascular risk was actually accounted for by other comorbidity variables in the models for DDKT recipients, while in the LDKT cohort with a significantly lower prevalence of other comorbidities, diabetes may have served as more general marker of poorer outcomes. A recent large population cohort study in Australia and New Zealand demonstrated that patients with Type 2 diabetes had significantly poorer survival after kidney transplantation, with the highest risk being among younger patients under the age of 40 years.44 In our study the LDKT population was significantly younger than the DDKT population and this may explain why diabetes was a significant risk factor in this population. The 5.6% higher risk of transplant failure among patients with diabetes (and 12% higher risk for patients with heart failure discussed previously) must be given due consideration in the context of LDKT, given the potential implications for both the recipient as well as the live donor.

A major strength of the present study is that it is a prospective and comprehensive analysis of a large cohort of transplant recipients from all UK transplant centres. The cohort included a large proportion of the national adult transplant population with a minimal amount of missing data, which adds to the reliability of the study. There are a number of limitations to this study. First, for practical reasons we used relatively broad definitions for each comorbidity and were unable to distinguish between differing levels of severity or duration for each condition. All comorbidity data were collected at the time of transplantation when patients were recruited to the study. Therefore, we were unable to assess the progression or improvement of each condition after transplantation, and whether this impacted on outcomes. Secondly, it should be noted that the study population is largely of white ethnicity and thus conclusions with respect to other ethnic groups may be less certain. Thirdly, due to the favourable survival outcomes of LDKT recipients, we were only able to analyse the composite outcome of transplant survival in this cohort, as there were too few events for separate analysis of graft and patient survival. Transplant survival (also known as graft survival not censored for death) is a commonly analysed end-point in the transplant literature, as it demonstrates the overall success of a transplant.45, 46 However, in the DDKT analysis we found that this method masked the importance of several comorbidity risk factors that were found to be significant when analysing graft and patient survival separately. Therefore, it is important that we carry out separate graft and patient survival analyses in the LDKT cohort after longer follow-up time. Finally, the results from this study describe associations and no causation can be inferred.

This study quantifies the risks associated with specific comorbid conditions in the context of kidney transplantation. The findings can be utilised in everyday clinical practice to fully inform patients of their individual risks and outcomes, to inform future wait-listing and allocation policy and also to guide further research into improving the outcomes of patients with specific comorbidities.

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**References**

1. Hsu CY, Iribarren C, McCulloch CE*, et al.* Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009; **169:** 342-350.

2. Longenecker JC, Coresh J, Powe NR*, et al.* Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. *J Am Soc Nephrol* 2002; **13:** 1918-1927.

3. Alani H, Tamimi A, Tamimi N. Cardiovascular co-morbidity in chronic kidney disease: Current knowledge and future research needs. *World Journal of Nephrology* 2014; **3:** 156-168.

4. NHS Blood and Transplant. UK Transplant Registry. Organ Donation and Transplantation Annual Activity Report. Available from https://[www.odt.nhs.uk/statistics-and-reports/annual-activity-report/](http://www.odt.nhs.uk/statistics-and-reports/annual-activity-report/) (accessed 07/03/2019).

5. Wu C, Evans I, Joseph R*, et al.* Comorbid conditions in kidney transplantation: association with graft and patient survival. *J Am Soc Nephrol* 2005; **16:** 3437-3444.

6. Chang SH, Russ GR, Chadban SJ*, et al.* Trends in kidney transplantation in Australia and New Zealand, 1993-2004. *Transplantation* 2007; **84:** 611-618.

7. Weinhandl ED, Snyder JJ, Israni AK*, et al.* Effect of Comorbidity Adjustment on CMS Criteria for Kidney Transplant Center Performance. *Am J Transplant* 2009; **9:** 506-516.

8. Jassal SV, Schaubel DE, Fenton SSA. Baseline comorbidity in kidney transplant recipients: a comparison of comorbidity indices. *Am J Kidney Dis* 2005; **46:** 136-142.

9. Fabbian F, De Giorgi A, Manfredini F*, et al.* Impact of comorbidity on outcome in kidney transplant recipients: a retrospective study in Italy. *Intern Emerg Med* 2016; **11:** 825-832.

10. Grosso G, Corona D, Mistretta A*, et al.* Predictive value of the Charlson comorbidity index in kidney transplantation. *Transplant Proc* 2012; **44:** 1859-1863.

11. Kotwal S, Webster AC, Cass A*, et al.* Comorbidity recording and predictive power of comorbidities in the Australia and New Zealand dialysis and transplant registry compared with administrative data: 2000-2010. *Nephrology (Carlton, Vic)* 2016; **21:** 930-937.

12. Machnicki G, Pinsky B, Takemoto S*, et al.* Predictive Ability of Pretransplant Comorbidities to Predict Long-Term Graft Loss and Death. *Am J Transplant* 2009; **9:** 494-505.

13. Farrugia D, Cheshire J, Begaj I*, et al.* Death within the first year after kidney transplantation--an observational cohort study. *Transpl Int* 2014; **27:** 262-270.

14. Oniscu GC, Ravanan R, Wu D*, et al.* Access to Transplantation and Transplant Outcome Measures (ATTOM): study protocol of a UK wide, in-depth, prospective cohort analysis. *BMJ Open* 2016; **6**.

15. Venkat-Raman G, Tomson CR, Gao Y*, et al.* New primary renal diagnosis codes for the ERA-EDTA. *Nephrol Dial Transplant* 2012; **27:** 4414-4419.

16. Johnson RJ, Fuggle SV, O'Neill J*, et al.* Factors influencing outcome after deceased heart beating donor kidney transplantation in the United Kingdom: an evidence base for a new national kidney allocation policy. *Transplantation* 2010; **89:** 379-386.

17. World Health Organization. BMI Classification. Available from <http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi> (accessed 07/08/2019).

18. Laubender RP, Bender R. Estimating adjusted risk difference (RD) and number needed to treat (NNT) measures in the Cox regression model. *Stat Med* 2010; **29:** 851-859.

19. NHS Blood and Transplant. Organ Donation and Transplantation Acitivty Report 2012/13. Available from https://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/activity\_report\_2012\_13.pdf (accessed 30/01/2018).

20. NHS Blood and Transplant. Organ Donation and Transplantation Activity Report 2011/2012. Available from https://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/activity\_report\_2011\_12.pdf (accessed 30/01/2018).

21. Patel SI, Chakkera HA, Wennberg PW*, et al.* Peripheral arterial disease preoperatively may predict graft failure and mortality in kidney transplant recipients. *Vasc Med* 2017**:** 1358863x16689830.

22. Shishehbor MH, Aksut B, Poggio E*, et al.* Presence of peripheral artery disease in renal transplant outcomes - Don't throw the baby out with the bath water. *Vasc Med* 2017**:** 1358863x17703195.

23. Droupy S, Eschwege P, Hammoudi Y*, et al.* Consequences of iliac arterial atheroma on renal transplantation. *J Urol* 2006; **175:** 1036-1039.

24. Cassuto J, Babu S, Laskowski I. The survival benefit of kidney transplantation in the setting of combined peripheral arterial disease and end-stage renal failure. *Clin Transplant* 2016; **30:** 545-555.

25. Gill JS, Tonelli M, Johnson N*, et al.* The impact of waiting time and comorbid conditions on the survival benefit of kidney transplantation. *Kidney Int* 2005; **68:** 2345-2351.

26. Akolekar D, Oniscu GC, Forsythe JL. Variations in the assessment practice for renal transplantation across the United Kingdom. *Transplantation* 2008; **85:** 407-410.

27. Gore JL, Pham PT, Danovitch GM*, et al.* Obesity and outcome following renal transplantation. *Am J Transplant* 2006; **6:** 357-363.

28. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. *Transplantation* 2002; **73:** 70-74.

29. Hill CJ, Courtney AE, Cardwell CR*, et al.* Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2015; **30:** 1403-1411.

30. Lafranca JA, IJermans JN, Betjes MG*, et al.* Body mass index and outcome in renal transplant recipients: a systematic review and meta-analysis. *BMC Med* 2015; **13:** 111.

31. Hortal L, Fernandez A, Losada A*, et al.* Study of the cyclosporine concentration at 2 hours in stable renal transplant patients and relation to body mass index. *Transplant Proc* 2001; **33:** 3110-3111.

32. Siedlecki A, Foushee M, Curtis JJ*, et al.* The impact of left ventricular systolic dysfunction on survival after renal transplantation. *Transplantation* 2007; **84:** 1610-1617.

33. Seliger SL, Gillen DL, Longstreth WT, Jr.*, et al.* Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 2003; **64:** 603-609.

34. Kennedy R, Case C, Fathi R*, et al.* Does renal failure cause an atherosclerotic milieu in patients with end-stage renal disease? *Am J Med* 2001; **110:** 198-204.

35. Findlay MD, Thomson PC, MacIsaac R*, et al.* Risk factors and outcome of stroke in renal transplant recipients. *Clin Transplant* 2016; **30:** 918-924.

36. Lentine KL, Rey LAR, Kolli S*, et al.* Variations in the Risk for Cerebrovascular Events after Kidney Transplant Compared with Experience on the Waiting List and after Graft Failure. *Clinical Journal of the American Society of Nephrology : CJASN* 2008; **3:** 1090-1101.

37. de Mattos AM, Prather J, Olyaei AJ*, et al.* Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors. *Kidney Int* 2006; **70:** 757-764.

38. Abedini S, Holme I, Fellstrom B*, et al.* Cerebrovascular events in renal transplant recipients. *Transplantation* 2009; **87:** 112-117.

39. Oliveras A, Roquer J, Puig JM*, et al.* Stroke in renal transplant recipients: epidemiology, predictive risk factors and outcome. *Clin Transplant* 2003; **17:** 1-8.

40. Yu T-M, Lin C-C, Shu K-H*, et al.* Increased risk of hepatic complications in kidney transplantation with chronic virus hepatitis infection: A nationwide population-based cohort study. *Sci Rep* 2016; **6:** 21312.

41. Fabrizi F, Martin P, Dixit V*, et al.* Hepatitis C virus antibody status and survival after renal transplantation: meta-analysis of observational studies. *Am J Transplant* 2005; **5:** 1452-1461.

42. Fabrizi F, Dixit V, Martin P*, et al.* Hepatitis B and survival after renal transplant: meta‐analysis of observational studies. *J Viral Hepat* 2014; **21:** 542-550.

43. Cosio FG, Hickson LJ, Griffin MD*, et al.* Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. *Am J Transplant* 2008; **8:** 593-599.

44. Lim WH, Wong G, Pilmore HL*, et al.* Long-term outcomes of kidney transplantation in people with type 2 diabetes: a population cohort study. *The Lancet Diabetes & Endocrinology* 2017; **5:** 26-33.

45. European Best Practice Guidelines for Renal Transplantation (Part 2) IV.13 Analysis of patient and graft survival. *Nephrol Dial Transplant* 2002; **17:** 60-67.

46. OPTN/SRTR 2016 Annual Data Report: Preface. *Am J Transplant* 2018; **18:** 1-9.

**Tables**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1. Characteristics of the study cohort** | | | |
|  | **DDKT recipients**  **n=1288** | **LDKT recipients**  **n=812** | **p-value** |
| **Recipient variables** |  |  |  |
| Recipient age, years (median, IQR) | 54 (44 - 63) | 46 (34 - 56) | <0.0001 |
| Recipient age group, years (n, %) |  |  | <0.0001 |
| 18 – 34 | 132 (10.3) | 229 (28.2) |  |
| 35 – 49 | 369 (28.7) | 263 (32.4) |  |
| 50 – 64 | 543 (42.2) | 252 (31.0) |  |
| 65 – 75 | 244 (18.9) | 68 (8.4) |  |
| Recipient gender (n, %) |  |  | 0.267 |
| Male | 824 (64.0) | 500 (61.6) |  |
| Female | 464 (36.0) | 312 (38.4) |  |
| Recipient ethnicity (n, %) |  |  | 0.0002 |
| White | 1023 (79.7) | 707 (87.1) |  |
| Asian | 140 (10.9) | 62 (7.6) |  |
| Black | 96 (7.5) | 35 (4.3) |  |
| Other | 25 (2.0) | 8 (1.0) |  |
| Primary renal disease (n, %) |  |  | <0.0001 |
| Polycystic kidney disease | 219 (17.0) | 112 (13.9) |  |
| Diabetic nephropathy | 134 (10.4) | 48 (5.9) |  |
| Glomerulonephritis | 320 (24.9) | 232 (28.7) |  |
| Pyelonephritis | 138 (10.7) | 128 (15.8) |  |
| Hypertensive nephropathy | 89 (6.9) | 37 (4.6) |  |
| Renal vascular disease | 29 (2.3) | 9 (1.1) |  |
| Other | 163 (12.7) | 85 (10.5) |  |
| Uncertain | 194 (15.1) | 157 (19.4) |  |
| Time on dialysis (n, %) |  |  | <0.0001 |
| Pre-emptive | 137 (10.6) | 279 (34.4) |  |
| 0 - 1 year | 160 (12.4) | 198 (24.4) |  |
| 1 - 3 years | 366 (28.4) | 185 (22.8) |  |
| 3 - 5 years | 295 (22.9) | 78 (9.6) |  |
| > 5 years | 330 (25.6) | 72 (8.9) |  |
| Previous transplant (n, %) | 165 (12.9) | 117 (14.5) | 0.297 |
| Highly sensitised, cRF≥85% (n, %) | 126 (9.8) | 95 (11.7) | 0.163 |
| Smoking status (n, %) |  |  | 0.702 |
| Non-smoker | 137 (11.7) | 78 (10.7) |  |
| Ex-smoker | 325 (27.7) | 212 (29.2) |  |
| Smoker | 710 (60.6) | 437 (60.1) |  |
| **Donor variables** |  |  |  |
| Donor age, years (median, IQR) | 54 (43 - 64) | 48 (39 - 57) | <0.0001 |
| Donor age group, years (n, %) |  |  | <0.0001 |
| <18 | 31 (2.4) | 0 |  |
| 18 – 34 | 160 (12.4) | 143 (17.6) |  |
| 35 – 49 | 303 (23.5) | 298 (36.7) |  |
| 50 – 64 | 512 (39.8) | 308 (37.9) |  |
| 65 – 75 | 234 (18.2) | 61 (7.5) |  |
| >75 | 48 (3.7) | 2 (0.3) |  |
| Donor gender (n, %) |  |  | 0.001 |
| Male | 696 (54.0) | 379 (46.7) |  |
| Female | 592 (46.0) | 432 (53.3) |  |
| Donor ethnicity (n, %) |  |  | <0.0001 |
| White | 1208 (95.2) | 720 (88.7) |  |
| Asian | 21 (1.7) | 52 (6.4) |  |
| Black | 23 (1.8) | 28 (3.5) |  |
| Other | 17 (1.3) | 12 (1.5) |  |
| Donor BMI, kg/m2 (n, %) |  |  | <0.0001 |
| Underweight (<18.5) | 0 | 0 |  |
| Normal (18.5 - 24.9) | 463 (37.3) | 254 (32.9) |  |
| Overweight (25.0 - 29.9) | 494 (39.7) | 390 (50.5) |  |
| Obese (≥30.0) | 286 (23.0) | 128 (16.6) |  |
| **Transplant variables** |  |  |  |
| HLA MM level (n, %) |  |  | <0.0001 |
| 1 | 155 (12.0) | 91 (11.2) |  |
| 2 | 355 (27.6) | 105 (12.9) |  |
| 3 | 679 (52.7) | 360 (44.3) |  |
| 4 | 99 (7.7) | 256 (31.5) |  |
| CIT, hours (median, IQR) | 14.5 (11.4 - 17.3) | 3.3 (2.4 - 4.1) | <0.0001 |
| Delayed graft function (n, %) | 378 (31.1) | 30 (3.9) | <0.0001 |
| DDKT; deceased-donor kidney transplant, LDKT; living-donor kidney transplant, IQR; interquartile range, cRF; calculated reaction frequency, BMI; body mass index, HLA MM; human leukocyte antigen mismatch, CIT; cold ischaemia time. Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Supplementary Table S2. | | | |

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| **Table 2. Prevalence of recipient comorbidity** | | | |
|  | **DDKT recipients**  **n=1288** | **LDKT recipients**  **n=812** | **p-value** |
| Diabetes (n, %) | 205 (16.0) | 83 (10.3) | 0.0002 |
| Ischaemic heart disease (n, %) | 126 (9.8) | 57 (7.0) | 0.029 |
| Heart failure (n, %) | 40 (3.1) | 13 (1.6) | 0.033 |
| Atrial fibrillation (n, %) | 25 (1.9) | 12 (1.5) | 0.434 |
| Cardiac valve replacement (n, %) | 10 (0.8) | 8 (1.0) | 0.609 |
| Pacemaker (n, %) | 10 (0.8) | 5 (0.6) | 0.673 |
| Cerebrovascular disease (n, %) | 75 (5.8) | 25 (3.1) | 0.004 |
| Peripheral vascular disease (n, %) | 43 (3.3) | 14 (1.7) | 0.027 |
| Abdominal aortic aneurysm (n, %) | 4 (0.3) | 2 (0.3) | 0.790 |
| Chronic respiratory disease (n, %) | 108 (8.4) | 59 (7.3) | 0.359 |
| Chronic liver disease (n, %) | 25 (1.9) | 14 (1.7) | 0.722 |
| Blood borne viruses (n, %) | 38 (3.0) | 13 (1.6) | 0.051 |
| Malignancy (n, %) | 93 (7.2) | 49 (6.1) | 0.294 |
| Mental illness (n, %) | 75 (5.8) | 41 (5.1) | 0.453 |
| BMI, kg/m2 (n, %) |  |  | 0.121 |
| Underweight (<18.5) | 26 (2.1) | 23 (3.0) |  |
| Normal (18.5 - 24.9) | 461 (37.5) | 312 (40.8) |  |
| Overweight (25.0 - 29.9) | 462 (37.6) | 282 (36.9) |  |
| Obese (≥30.0) | 281 (22.9) | 147 (19.2) |  |
| Number of comorbidities (n, %) |  |  | 0.002 |
| 0 | 573 (46.7) | 414 (54.4) |  |
| 1 - 2 | 579 (47.2) | 316 (41.5) |  |
| ≥3 | 74 (6.0) | 31 (4.1) |  |
| DDKT; deceased-donor kidney transplant, LDKT; living-donor kidney transplant, BMI; body mass index. Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Supplementary Table S2. | | | |

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| **Table 3. Cox regression analysis for impact of comorbidity on 2-year survival outcomes of deceased donor kidney transplants** | | | | | | |
|  | **Transplant survival model** | | **Graft survival model** | | **Patient survival model** | |
| **Variables** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Recipient comorbidity** |  |  |  |  |  |  |
| Heart failure | 2.39 (1.30, 4.37) | 0.005 | - | - | 3.77 (1.79, 7.95) | 0.0005 |
| Cerebrovascular disease | 2.33 (1.40, 3.88) | 0.001 | - | - | 3.45 (1.72, 6.92) | 0.0005 |
| Chronic liver disease | - | - | - | - | 4.36 (1.29, 14.71) | 0.018 |
| Peripheral vascular disease | - | - | 3.04 (1.37, 6.74) | 0.006 | - | - |
| BMI, kg/m2 |  |  |  |  |  |  |
| Underweight (<18.5) | - | - | 0.86 (0.11, 6.49) | 0.885 | - | - |
| Normal (18.5 - 24.9) | - | - | 1 (reference) |  | - | - |
| Overweight (25.0 - 29.9) | - | - | 1.48 (0.84, 2.61) | 0.180 | - | - |
| Obese (≥30.0) | - | - | 2.27 (1.27, 4.06) | 0.006 | - | - |
| **Other variables** |  |  |  |  |  |  |
| Time on dialysis (years) |  |  |  |  |  |  |
| < 3 | 1 (reference) |  | 1 (reference) |  | 1 (reference) |  |
| ≥ 3 | 2.08 (1.41, 3.08) | 0.0002 | 1.84 (1.11, 3.04) | 0.018 | 2.47 (1.36, 4.50) | 0.003 |
| Recipient age (per 10 years) | 1.10 (0.92, 1.30) | 0.290 | 0.84 (0.68, 1.05) | 0.128 | 1.67 (1.23, 2.25) | 0.0009 |
| Recipient ethnicity |  |  |  |  |  |  |
| White | 1 (reference) |  | 1 (reference) |  | - | - |
| Asian | 0.67 (0.35, 1.29) | 0.228 | 0.76 (0.35, 1.69) | 0.504 | - | - |
| Black | 1.23 (0.68, 2.21) | 0.495 | 1.52 (0.77, 3.02) | 0.228 | - | - |
| Other | 0.37 (0.05, 2.63) | 0.317 | 0.62 (0.08, 4.53) | 0.636 | - | - |
| Highly sensitised (cRF≥85%) | 1.47 (0.87, 2.47) | 0.153 | 2.22 (1.18, 4.19) | 0.014 | - | - |
| Donor age (per 10 years) | 1.14 (0.99, 1.31) | 0.066 | 1.23 (1.02, 1.48) | 0.028 | 1.11 (0.89, 1.39) | 0.349 |
| HLA MM level |  |  |  |  |  |  |
| 1 | 1 (reference) |  | 1 (reference) |  | 1 (reference) |  |
| 2 | 1.18 (0.62, 2.27) | 0.612 | 2.94 (1.08, 7.98) | 0.035 | 0.40 (0.16, 1.01) | 0.052 |
| 3 | 1.05 (0.57, 1.94) | 0.866 | 2.25 (0.85, 5.93) | 0.103 | 0.46 (0.21, 1.01) | 0.051 |
| 4 | 1.25 (0.53, 2.93) | 0.612 | 2.78 (0.81, 9.59) | 0.106 | 0.66 (0.22, 2.01) | 0.467 |
| Cold ischaemia time (per hour) | 1.04 (1.01, 1.08) | 0.028 | 1.01 (0.97, 1.06) | 0.568 | 1.04 (0.99, 1.10) | 0.118 |
| HR; hazard ratio, CI; confidence interval, BMI; body mass index, cRF; calculated reaction frequency, HLA MM; human leukocyte antigen mismatch. | | | | | | |

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| **Table 4. Kaplan-Meier estimates for 2-year graft survival of deceased-donor kidney transplants** | | |
| **Comorbidity** | **Survival (95% CI)** | **p-value** |
| Peripheral vascular disease |  | 0.006 |
| No | 93.6 (92.0, 94.8) |  |
| Yes | 83.5 (68.5, 91.8) |  |
| BMI, kg/m2 |  | 0.012 |
| Normal (18.5 - 24.9) | 95.2 (92.7, 96.8) |  |
| Obese (≥30.0) | 90.1 (85.9, 93.1) |  |

p-value is for log-rank test.

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| **Table 5. Cause of graft failure among DDKT cohort** | | | |
| **Cause of graft failure** | **All patients** | **Obese patients** | **PVD patients** |
| Acute rejection | 26 (34.2%) | 11 (44.0%) | 1 (14.3%) |
| Vascular thrombosis | 6 (7.9%) | 0 (0%) | 1 (14.3%) |
| Technical operative issues | 9 (11.8%) | 3 (12.0%) | 3 (42.9%) |
| Non-viable kidney | 9 (11.8%) | 3 (12.0%) | 1 (14.3%) |
| Infection | 1 (1.3%) | 0 (0%) | 0 (0%) |
| Recurrent primary renal disease | 4 (5.3%) | 0 (0%) | 0 (0%) |
| Other | 21 (27.6%) | 8 (32.0%) | 1 (14.3%) |

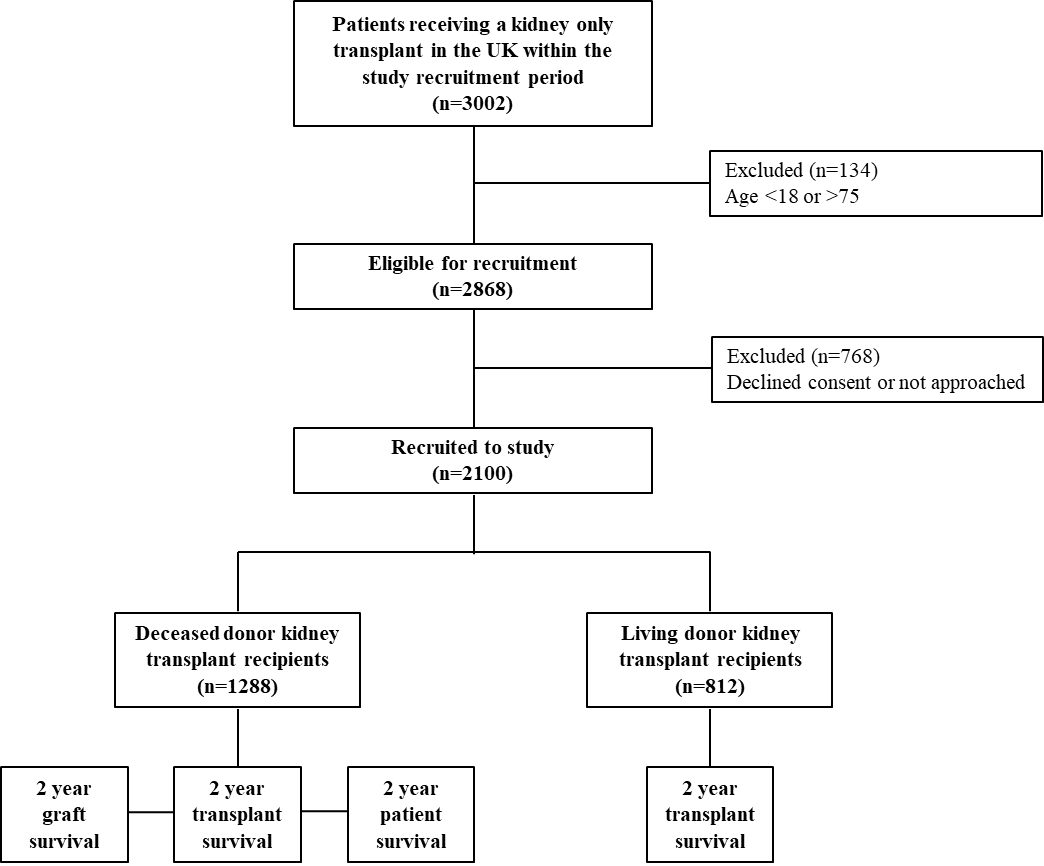
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| **Table 6. Kaplan-Meier estimates for 2-year patient survival after deceased-donor kidney transplantation** | | |
| **Comorbidity** | **Survival (95% CI)** | **p-value** |
| Heart failure |  | <0.0001 |
| No | 96.0 (94.8, 97.0) |  |
| Yes | 75.8 (58.5, 86.7) |  |
| Cerebrovascular disease |  | <0.0001 |
| No | 96.2 (94.9, 97.1) |  |
| Yes | 82.7 (71.5, 89.8) |  |
| Chronic liver disease |  | 0.003 |
| No | 95.7 (94.3, 96.7) |  |
| Yes | 83.6 (62.0, 93.5) |  |

p-value is for log-rank test.

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| **Table 7. Cox regression analysis for impact of comorbidity on 2-year transplant survival of living-donor kidney transplants** | | |
| **Variables** | **HR (95% CI)** | **p-value** |
| **Recipient comorbidity** |  |  |
| Heart failure | 3.83 (1.15, 12.81) | 0.029 |
| Diabetes | 2.23 (1.03, 4.81) | 0.042 |
| **Other variables** |  |  |
| Time on dialysis (years) |  |  |
| < 3 | 1 (reference) |  |
| ≥ 3 | 2.16 (1.13, 4.11) | 0.019 |
| Recipient age (per 10 years) | 1.01 (0.80, 1.28) | 0.926 |
| Donor age (per 10 years) | 1.03 (0.81, 1.31) | 0.828 |
| HLA MM level |  |  |
| 1 | 1 (reference) |  |
| 2 | 0.76 (0.23, 2.51) | 0.657 |
| 3 | 0.74 (0.29, 1.86) | 0.520 |
| 4 | 0.67 (0.25, 1.82) | 0.428 |
| HR; hazard ratio, CI; confidence interval, HLA MM; human leukocyte antigen mismatch. | | |

**Figures**

**Figure 1. Study population and analyses**

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Patients were recruited from all 23 UK renal transplant centres. Recruitment took place over a 12-month period in each centre, between 1st November 2011 and 31st March 2013

**Figure 2. Kaplan-Meier curves for 2-year graft survival of deceased-donor kidney transplants**

1. **Peripheral vascular disease (PVD)**

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1. **Body mass index (BMI)**

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**Figure 3. Kaplan-Meier curves for 2-year patient survival after deceased-donor kidney transplantation**

**A. Heart failure (HF)**

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**B. Cerebrovascular disease (CVD)**

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1. **Chronic liver disease (CLD)**

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**Supplementary Material**

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| **Table S1. Comorbidity variable definitions** | |
| **Comorbidity** | **Definition (presence of any of the following)** |
| Diabetes | * Any cause of diabetes * Type I diabetes – Insulin required from time of diagnosis * Type II diabetes – Treatment with diet-control, oral antidiabetic medication or insulin |
| Ischaemic heart disease | * Angina – chest pain on exertion, relieved by rest or Glyceryl Trinitrate. As reported by patient or as documented in the case notes, with or without ECG changes, exercise tolerance testing or other imaging * Non-ST segment elevation myocardial infarction (NSTEMI) – troponin rise and non-ST segment elevation ischaemic ECG changes such as ST depression, T-wave inversion or no ECG changes. * ST segment elevation myocardial infarction (STEMI) – troponin rise and ST segment elevation on ECG. * Percutaneous coronary intervention (coronary angioplasty with or without stent insertion) * Coronary artery bypass graft operation |
| Heart failure | * Congestive cardiac failure * Left ventricular failure * Right ventricular failure * Left or right ventricular dysfunction on cardiac echo * Ejection fraction <30% on cardiac echo |
| Atrial fibrillation | * Patients in chronic atrial fibrillation at the time of recruitment, previous isolated episodes not included |
| Cardiac valve replacement | * Any kind of cardiac valve replacement or repair |
| Pacemaker | * Permanent pacemaker in-situ |
| Cerebrovascular disease | * Transient ischaemic attack (TIA) – also known as “mini-stroke”. Transient episode of neurologic dysfunction caused by ischaemia without infarction. Symptoms typically lasting less than 24 hours. * Cerebrovascular accident (CVA) including:   + Ischaemic stroke   + Cerebral haemorrhage   + Subarachnoid haemorrhage   + Subdural haemorrhage * Previous carotid intervention including:   + Carotid endarterectomy   + Carotid angioplasty |
| Peripheral vascular disease | * Claudication – lower limb pain on walking as reported by the patient, with or without doppler or angiographic evidence. * Radiological diagnosis * Radiological or surgical intervention including:   + Angioplasty   + Endarterectomy   + Bypass graft   + Amputation of any part of limb |
| Abdominal aortic aneurysm | * Radiological diagnosis under surveillance * Previous endovascular aneurysm repair * Previous open surgical repair |
| Chronic respiratory disease | * Any kind of chronic respiratory disease including: * Asthma – inflammatory condition of the lungs causing recurrent attacks of breathlessness and wheezing, differs in severity and occurs in all age groups. * Chronic obstructive pulmonary disease (COPD) – chronic and progressive airflow obstruction that is not fully reversible. FEV1/FVC ratio <0.7 and FEV1 < 80% predicted. * Bronchiectasis – abnormal and irreversible dilatation of the bronchi due to destruction of elastic and muscular tissue by acute or chronic inflammation and infection. Results in chronic infections and airway obstruction. |
| Chronic liver disease | * Persistent enzyme evidence of hepatic dysfunction with imaging or biopsy evidence of cirrhotic or non-cirrhotic liver disease * Excludes cholecystitis or gallstones |
| Blood borne viruses | * Hepatitis C * Hepatitis B * HIV |
| Malignancy | * Diagnosis of any malignancy in the past or in the present. Does not include benign tumours such as breast adenoma, colon polyp, actinic keratosis etc. |
| Mental illness | * Any diagnosis of mental illness e.g. depression, psychosis, bipolar disorder, substance abuse, deliberate self-harm, schizophrenia |
| Data for comorbidities were extracted from patient case notes, local electronic patient information systems and/or confirmed with the patients named consultant nephrologist at the time of recruitment to ATTOM. | |

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| **Table S2. Missing data** | | |
| **Variables** | **DDKT recipients**  **n=1288** | **LDKT recipients**  **n=812** |
| **Recipient variables** |  |  |
| Recipient age | 0 | 0 |
| Recipient gender | 0 | 0 |
| Recipient ethnicity | 4 (0.31%) | 0 |
| Primary renal disease | 2 (0.16%) | 4 (0.49%) |
| Time on dialysis | 0 | 0 |
| Previous transplant | 7 (0.54%) | 4 (0.49%) |
| Sensitisation level | 0 | 0 |
| Smoking status | 116 (9.0%) | 85 (10.5%) |
| **Donor variables** |  |  |
| Donor age | 0 | 0 |
| Donor gender | 0 | 1 (0.12%) |
| Donor ethnicity | 19 (1.48%) | 0 |
| Donor BMI | 45 (3.49%) | 40 (4.93%) |
| **Transplant variables** |  |  |
| HLA MM level | 0 | 0 |
| CIT (per hour) | 17 (1.32%) | 66 (8.13%) |
| **Recipient comorbidity variables** |  |  |
| Diabetes | 3 (0.23%) | 2 (0.25%) |
| Ischaemic heart disease | 3 (0.23%) | 2 (0.25%) |
| Heart failure | 2 (0.16%) | 2 (0.25%) |
| Atrial fibrillation | 2 (0.16%) | 2 (0.25%) |
| Cardiac valve replacement | 3 (0.23%) | 4 (0.49%) |
| Pacemaker | 2 (0.16%) | 3 (0.37%) |
| Cerebrovascular disease | 2 (0.16%) | 3 (0.37%) |
| Peripheral vascular disease | 2 (0.16%) | 3 (0.37%) |
| Abdominal aortic aneurysm | 2 (0.16%) | 3 (0.37%) |
| Chronic respiratory disease | 2 (0.16%) | 2 (0.25%) |
| Chronic liver disease | 2 (0.16%) | 2 (0.25%) |
| Blood borne viruses | 3 (0.23%) | 2 (0.25%) |
| Malignancy | 2 (0.16%) | 2 (0.25%) |
| Mental illness | 2 (0.16%) | 2 (0.25%) |
| BMI | 58 (4.50%) | 48 (5.91%) |
| **Outcome variables** |  |  |
| Delayed graft function | 74 (5.7%) | 49 (6.0%) |
| Graft survival | 2 (0.16%) | 3 (0.37%) |
| Patient survival | 1 (0.08%) | 3 (0.37%) |
| Cause of graft failure | 9 (10.58%) | 2 (7.69%) |
| DDKT; Deceased-donor kidney transplant, LDKT; Living-donor kidney transplant, BMI; body mass index, CIT; cold ischaemia time.  Data are number (%). | | |

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| **Table S3. Demographics of excluded vs recruited kidney transplant recipients** | | | | | |
| Variable |  | Excluded (%) | Recruited (%) | | p-value |
| Age group | |  |  | | 0.307 |
| 18 – 34 | | 15.5 | 17.2 | |  |
| 35 – 49 | | 29.0 | 30.1 | |  |
| 50 – 64 | | 38.0 | 37.9 | |  |
| 65 – 75 | | 17.4 | 14.9 | |  |
| Gender | |  |  | | 0.332 |
| Male | | 61.1 | 63.0 | |  |
| Female | | 38.9 | 37.0 | |  |
| Ethnicity | |  |  | | 0.001 |
| White | | 76.0 | 82.4 | |  |
| Asian | | 13.5 | 9.6 | |  |
| Black | | 7.4 | 6.2 | |  |
| Other | | 2.3 | 1.6 | |  |
| Missing | | 0.7 | 0.2 | |  |
| Type of transplant | |  |  | | 0.253 |
| LD | | 36.3 | 38.7 | |  |
| DD | | 63.7 | 61.3 |  | |

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| **Table S4. Cox regression analysis for impact of comorbidity and delayed graft function on 2-year survival outcomes of deceased donor kidney transplants** | | | | | | |
|  | **Transplant survival model** | | **Graft survival model** | | **Patient survival model** | |
| **Variables** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Recipient comorbidity** |  |  |  |  |  |  |
| Heart failure | 2.77 (1.50, 5.12) | 0.001 | - | - | 3.86 (1.82, 8.20) | 0.0004 |
| Cerebrovascular disease | 2.05 (1.17, 3.59) | 0.012 | - | - | 3.50 (1.73, 7.08) | 0.0005 |
| Chronic liver disease | - | - | - | - | 4.68 (1.39, 15.79) | 0.013 |
| Peripheral vascular disease | - | - | 2.58 (1.01, 6.59) | 0.047 | - | - |
| BMI, kg/m2 |  |  |  |  |  |  |
| Underweight (<18.5) | - | - | 1.52 (0.19, 11.67) | 0.688 | - | - |
| Normal (18.5 - 24.9) | - | - | 1 (reference) |  | - | - |
| Overweight (25.0 - 29.9) | - | - | 1.96 (1.01, 3.78) | 0.046 | - | - |
| Obese (≥30.0) | - | - | 2.83 (1.43, 5.62) | 0.003 | - | - |
| **Other variables** |  |  |  |  |  |  |
| Delayed graft function | 1.75 (1.19, 2.56) | 0.004 | 1.86 (1.12, 3.09) | 0.017 | 1.24 (0.70, 2.20) | 0.463 |
| Time on dialysis (years) |  |  |  |  |  |  |
| < 3 | 1 (reference) |  | 1 (reference) |  | 1 (reference) |  |
| ≥ 3 | 2.06 (1.35, 3.13) | 0.0008 | 2.02 (1.15, 3.55) | 0.014 | 2.26 (1.24, 4.15) | 0.008 |
| Recipient age (per 10 years) | 1.06 (0.88, 1.28) | 0.528 | 0.81 (0.64, 1.03) | 0.086 | 1.56 (1.17, 2.15) | 0.0003 |
| Recipient ethnicity |  |  |  |  |  |  |
| White | 1 (reference) |  | 1 (reference) |  | - | - |
| Asian | 0.76 (0.39, 1.47) | 0.418 | 0.88 (0.40, 1.96) | 0.756 | - | - |
| Black | 0.83 (0.41, 1.67) | 0.598 | 1.10 (0.49, 2.46) | 0.826 | - | - |
| Other | 0.00 (0.00, 0.00) | . | 0.00 (0.00, 0.00) | . | - | - |
| Highly sensitised (cRF≥85%) | 1.52 (0.86, 2.67) | 0.151 | 2.35 (1.16, 4.77) | 0.018 | - | - |
| Donor age (per 10 years) | 1.09 (0.93, 1.27) | 0.280 | 1.14 (0.93, 1.40) | 0.208 | 1.07 (0.86, 1.35) | 0.538 |
| HLA MM level |  |  |  |  |  |  |
| 1 | 1 (reference) |  | 1 (reference) |  | 1 (reference) |  |
| 2 | 1.25 (0.61, 2.58) | 0.544 | 3.95 (1.14, 13.72) | 0.018 | 0.39 (0.15, 1.04) | 0.059 |
| 3 | 1.15 (0.58, 2.27) | 0.696 | 2.94 (0.86, 9.97) | 0.084 | 0.51 (0.23, 1.16) | 0.107 |
| 4 | 1.03 (0.38, 2.79) | 0.951 | 2.19 (0.42, 11.42) | 0.323 | 0.74 (0.24, 2.33) | 0.608 |
| Cold ischaemia time (per hour) | 1.03 (0.99, 1.07) | 0.105 | 1.02 (0.95, 1.06) | 0.940 | 1.05 (0.99, 1.11) | 0.102 |
| HR; hazard ratio, CI; confidence interval, BMI; body mass index, cRF; calculated reaction frequency, HLA MM; human leukocyte antigen mismatch. | | | | | | |

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| **Table S5. Cox regression analysis for impact of BMI on 2-year graft survival of deceased donor kidney transplants** | | | |
| **BMI (kg/m2)** | **n** | **HR (95% CI)** | **p-value** |
| Underweight (<18.5) | 26 | 0.88 (0.11, 6.49) | 0.885 |
| Normal (18.5 - 24.9) | 461 | 1 (reference) |  |
| Overweight (25.0 - 29.9) | 462 | 1.48 (0.84, 2.61) | 0.180 |
| Obese class I (30.0 - 34.9) | 222 | 2.29 (1.23, 4.26) | 0.009 |
| Obese class II/III (≥35.0) | 59 | 2.19 (0.87, 5.46) | 0.094 |
| Model adjusted for peripheral vascular disease, time on dialysis, recipient age, recipient ethnicity, highly sensitised (cRF≥85%), donor age, HLA MM level and cold ischaemia time. | | | |

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| **Table S6. Cox regression model for 2-year transplant survival of deceased-donor kidney transplants (including risk score)** | | |
| **Variables** | **HR (95% CI)** | **p-value** |
| Heart failure | 2.38 (1.30, 4.34) | 0.005 |
| Cerebrovascular disease | 2.21 (1.34, 3.67) | 0.002 |
| Time on dialysis (years) |  |  |
| < 3 | 1 (reference) |  |
| ≥ 3 | 2.17 (1.49, 3.16) | <0.0001 |
| Risk score (per unit) | 1.11 (1.03, 1.19) | 0.005 |
| HR; hazard ratio, CI; confidence interval.  Model is adjusted for a risk score (Box S1) that incorporates relevant confounding variables. | | |

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| **Box S1. Risk score for 2-year transplant survival based on UK transplant registry data for deceased-donor kidney transplants in 2006 - 2011 (n=6469)**  Transplant survival risk score = exp [ - 0.3687 if recipient age 30-39  - 0.3885 if recipient age 40-49  - 0.2020 if recipient age 50-59  - 0.1863 if recipient age 60-64  + 0.1589 if recipient age is 65-75  + 0.1808 if recipient ethnicity Asian  + 0.2745 if recipient ethnicity Black  - 0.5727 if recipient ethnicity Other  + 0.2494 if recipient highly sensitised (cRF≥85%)  + 0.02475 x donor age  - 0.2978 if HLA MM level 1  + 0.1518 if HLA MM level 3  - 0.07197 if HLA MM level 4  + 0.00613 x cold ischaemic time in hours ] |

exp; exponential function, HLA MM; human leukocyte antigen mismatch, cRF; calculated reaction frequency. HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section). “Other” is any ethnicity other than White, Asian or Black.

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| **Table S7. Cox regression model for 2-year graft survival of deceased-donor kidney transplants (including risk score)** | | |
| **Variables** | **HR (95% CI)** | **p-value** |
| Peripheral vascular disease | 2.74 (1.25, 5.99) | 0.012 |
| BMI, kg/m2 |  |  |
| Underweight (<18.5) | 0.97 (0.13, 7.23) | 0.977 |
| Normal (18.5 - 24.9) | 1 (reference) |  |
| Overweight (25.0 - 29.9) | 1.33 (0.76, 2.34) | 0.319 |
| Obese (≥30.0) | 2.14 (1.20, 3.80) | 0.010 |
| Time on dialysis (years) |  |  |
| < 3 | 1 (reference) |  |
| ≥ 3 | 2.08 (1.29, 3.35) | 0.003 |
| Risk score (per unit) | 1.21 (1.07, 1.37) | 0.003 |
| HR; hazard ratio, CI; confidence interval, BMI; body mass index.  Model is adjusted for a risk score (Box S2) that incorporates relevant confounding variables. | | |

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| **Box S2. Risk score for 2-year graft survival based on UK transplant registry data for deceased-donor kidney transplants in 2006 - 2011 (n=5569)**  Graft survival risk score = exp [ - 0.5205 if recipient age 30-39  - 0.6398 if recipient age 40-49  - 0.5586 if recipient age 50-59  - 0.6910 if recipient age 60-64  - 0.4789 if recipient age is 65-75  + 0.1503 if recipient ethnicity Asian  + 0.2982 if recipient ethnicity Black  - 0.6247 if recipient ethnicity Other  + 0.02813 x donor age  - 0.1626 if HLA MM level 1  + 0.2599 if HLA MM level 3  - 0.06468 if HLA MM level 4  + 0.00347 x cold ischaemic time in hours ] |

exp; exponential function, HLA MM; human leukocyte antigen mismatch. HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section). “Other” is any ethnicity other than White, Asian or Black.

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| **Table S8. Cox regression model for 2-year patient survival of deceased-donor kidney transplants (including risk score)** | | |
| **Variables** | **HR (95% CI)** | **p-value** |
| **Comorbidity** |  |  |
| Heart failure | 3.72 (1.76, 7.87) | 0.0006 |
| Cerebrovascular disease | 3.37 (1.69, 6.71) | 0.0005 |
| Chronic liver disease | 3.94 (1.21, 12.83) | 0.023 |
| Time on dialysis (years) |  |  |
| < 3 | 1 (reference) |  |
| ≥ 3 | 2.34 (1.30, 4.22) | 0.005 |
| Risk score (per unit) | 1.02 (1.01, 1.03) | 0.0009 |
| HR; hazard ratio, CI; confidence interval.  Model is adjusted for a risk score (Box S3) that incorporates relevant confounding variables. | | |

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| **Box S3. Risk score for 2-year patient survival based on UK transplant registry data for deceased-donor kidney transplants in 2006 - 2011 (n=5569)**  Patient survival risk score = exp [ - 0.8798 if recipient age 30-39  + 1.4404 if recipient age 40-49  + 1.8680 if recipient age 50-59  + 2.1586 if recipient age 60-64  + 2.8002 if recipient age is 65-75  + 0.01730 x donor age  - 0.4345 if HLA MM level 1  - 0.01808 if HLA MM level 3  - 0.1475 if HLA MM level 4  + 0.01632 x cold ischaemic time in hours ] |

exp; exponential function, HLA MM; human leukocyte antigen mismatch. HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section).

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| **Table S9. Cox regression model for 2-year transplant survival of living-donor kidney transplants (including risk score)** | | |
| **Variables** | **HR (95% CI)** | **p-value** |
| **Comorbidity** |  |  |
| Heart failure | 3.63 (1.10, 11.97) | 0.035 |
| Diabetes | 2.21 (1.05, 4.66) | 0.037 |
| **Other variables** |  |  |
| Time on dialysis (years) |  |  |
| < 3 | 1 (reference) |  |
| ≥ 3 | 2.20 (1.16, 4.16) | 0.016 |
| Risk score (per unit) | 1.02 (0.46, 2.23) | 0.968 |
| HR; hazard ratio, CI; confidence interval.  Diabetes includes any diagnosis of diabetes (both as a primary renal disease and a comorbidity).  Model is adjusted for a risk score (Box S4) that incorporates relevant confounding variables. | | |

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| **Box S4. Risk score for 2-year transplant survival based on UK transplant registry data for living-donor kidney transplants in 2006 - 2011 (n=3837)**  Transplant survival risk score = exp [ - 0.1519 if recipient age 30-39  - 0.2066 if recipient age 40-49  - 0.4011 if recipient age 50-59  - 0.05848 if recipient age 60-64  + 0.3659 if recipient age is 65-75  + 0.00879 x donor age  - 0.07066 if HLA MM level 1  - 0.01556 if HLA MM level 3  - 0.2242 if HLA MM level 4 ] |

exp; exponential function, HLA MM; human leukocyte antigen mismatch. HLA MM is classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme (see Methods section).